

RNA surveillance: watching the defectives. Detecting premature stop codons in mRNA halts the production of dangerous truncated proteins

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Only those changes in DNA sequence that have functional consequences are known as disease-causing mutations. One such frequently occurring mutation causes a premature stop codon to appear in the middle of a protein-coding sequence of messenger RNA (mRNA). Stop codons (a triplet of nucleotides: UAA, UAG, or UGA) normally signal the end of the stretch of mRNA that is translated into protein so that when one appears early, the result can be a truncated protein that could have nasty consequences for the host organism.

However, a mechanism known as "nonsense-mediated decay" has evolved to detect these harmful RNAs, and [sequence analysis](http://www.ncbi.nlm.nih.gov/Coffeebreak/CB7_NMD/BQ1.html) [http://www.ncbi.nlm.nih.gov/Coffeebreak/CB7_NMD/BQ1.html] suggests that it may have been conserved in eukaryotic organisms, including humans [http://www.ncbi.nlm.nih.gov/genemap/map.cgi?MAP=GB4&BIN=562&MARK=A006H36].

In yeast, three proteins have been identified that are required to seek and destroy the partly translated RNAs: [Upf1p](#), [Upf2p](#), and [Upf3p](#).

[Upf1p](#) is an RNA unwinding enzyme, a helicase, that requires ATP for activity. Unfortunately, [Upf1p](#) will unwind pretty much anything, not just the problem mRNAs. So [Upf2p](#) and [Upf3p](#) are thought to be required to help [Upf1p](#) discriminate between nonsense and "real" mRNAs.

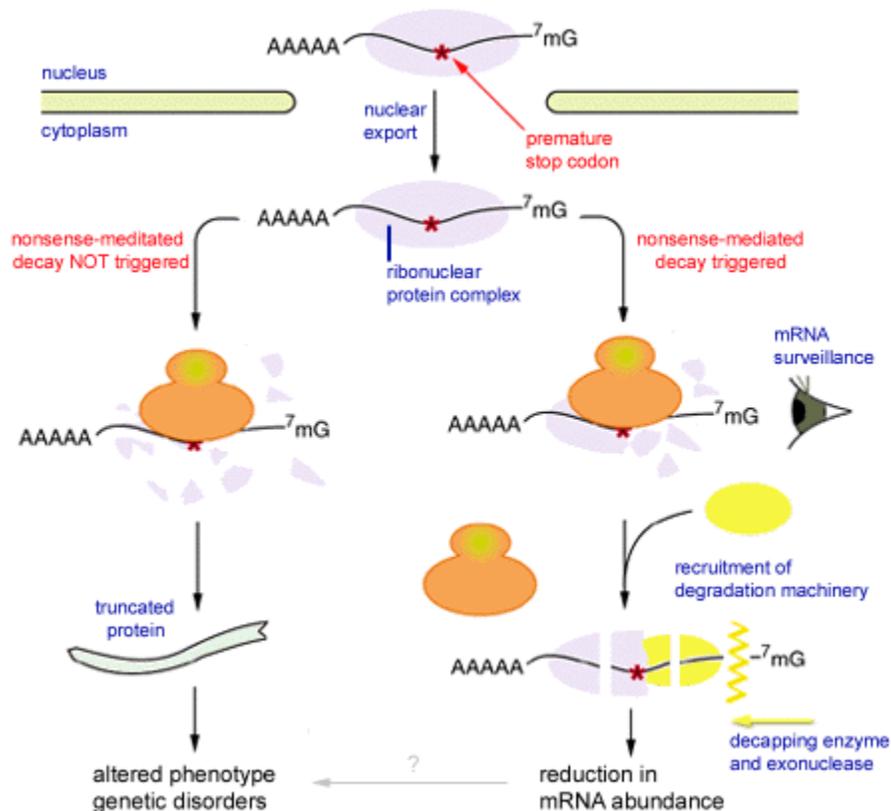
How do the core proteins work in synergy to trigger nonsense-mediated decay? One possibility is that [Upf3p](#), along with several other ribonuclear proteins, may first bind to an mRNA as it is being exported

from the nucleus en route to the ribosome, the site of protein synthesis. If the mRNA is fully translated into protein, [Upf3p](#) and the other protein factors are displaced. However, if there is a premature stop codon, [Upf3p](#) and cohorts may sit tight and mark the mutant mRNA as one that needs to be disposed of.

Experiments have shown that [Upf3p](#) can bind [Upf2p](#). Once bound, [Upf2p](#) could signal to the "termination complex", a mixed bag of termination factors that includes [Upf1p](#). This results in the release of the incomplete polypeptide from the ribosome, mRNA unwinding by [Upf1p](#) and, exposure of the mRNA for total degradation by exonuclease. Although this model is attractive, more experiments are required to show that this actually happens in a living yeast cell.

Many of the mutations that form a premature stop codon lead to human disease, for example, those in *BRCA1* that lead to breast cancer, or those in *NF1* that lead to neurofibromatosis type 1, to name just two. There are two ways by which nonsense-mediated decay can play a role in the disease process [http://www.ncbi.nlm.nih.gov/entrez/disposim.cgi?id=601430]. The first occurs when the machinery is functioning correctly: if mutant mRNAs are removed, then there will be a reduction in the amount of mRNA and protein available in the cell. The second is when a mutation occurs in the nonsense-mediated decay process itself, such as a mutation in *RENT1*, a human homolog of [Upf1p](#),

resulting in a population of truncated proteins, which could be harmful when targeted to their site of function.



Nonsense-mediated decay (NMD) in yeast, as a model for NMD in humans Ribonuclear proteins that bind to mRNAs in the nucleus remain associated with the mRNA as it becomes attached to the ribosome. When a premature stop codon is present, one of these proteins could be Upf3p. If Upf3p, or another as yet unidentified factor, is recognized by the surveillance complex (represented here by the eye), then the NMD mechanism is triggered. In yeast, this trigger may be assisted by the binding of Upf2p to Upf3p, after which the Upf1p helicase unwinds the mRNA, leaving it open for degradation by a decapping enzyme and exonuclease. Should the premature stop codon not be recognized, translation of the mRNA proceeds and results in the production of a truncated protein.

Important Links

Live PubMed searches

- (1) Upf1p
- (2) Nonsense mediated decay
- (3) Premature stop codon AND disease
- (4) REVIEWS

Related resources

GeneMap [<http://www.ncbi.nlm.nih.gov/genemap/map.cgi?MAP=GB4&BIN=562&MARK=A006H36>]
 OMIM
 LocusLink

Box: Use BLAST to search for relatives of yeast Upf1p

Click on the link below to start an html tutorial.

Find relatives of yeast Upf1p [http://www.ncbi.nlm.nih.gov/Coffeebreak/CB7_NMD/BQ1.html]